Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-9 and 11-21 are pending in the application, with claims 1 and 16 being the independent claims.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Objections

The Examiner has objected to claims 13-14 and 20 as being dependent upon a rejected base claim. The Examiner's objection will be moot upon allowance of said rejected base claims after reconsideration of the rejections in view of the provided arguments.

Rejections under 35 U.S.C. § 112

Claims 1-9, 11-12, 15-19, and 21 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Based on the Examiner's comments, it is respectfully submitted that the Examiner is confusing enablement issues with written description issues. Applicant has responded accordingly.

The Examiner has alleged that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner has stated that the specification teaches the production of double cross-linked HA, alleging that the support in the specification is not adequate for the claim to the production of multiple cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. The Examiner further alleges that the routine experimentation is not seen to be routine, stating that the specification does not provide any guidance as to forming a third or higher cross-link of HA. The Examiner has further stated that there are a great number of compounds which may be envisioned as being multiple cross-linked HA, each being produced by a process employing a certain degree of specificity for which there is not seen adequate support for in the instant disclosure. The Examiner has alleged that there is limited predictability in the art in regard to chemical reactivates [sic] of any functional group (i.e. solvent effects, temperature, stearic hindrance, pH, etc.), and that to provide adequate support for the breadth of the claims, Applicant would have to provide sufficient evidence showing the production of multiple cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. Applicant respectfully disagrees and traverses this rejection.

The Examiner has set forth a 35 U.S.C. §112, first paragraph, written description rejection, with the crux of the Examiner's rejection seeming to be the allegation that the experimentation that would have been required to practice the full scope of the claims would not have been routine, and that Applicant has not provided a representative

number of species for all of the possible compounds that fall under the full scope of the claims. In fulfilling the written description requirement of 35 U.S.C. §112, first paragraph, the specification of the application must demonstrate to the skilled artisan the Applicant has possession of the claimed invention at the time of filing. Purdue Pharma v. Faulding Inc., 230 F.3d 1320, 1323 (Fed. Cir. 2000).

The description only needs to describe in detail that which is new or not conventional. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). Information which is well known in the art need not be described in detail in the specification. Id. at 1379. Further, the MPEP sets forth recommended guidelines for determining compliance with the written description requirement: 1) determine what each claim as a whole covers; 2) review the entire application to understand how applicant provides support for the claimed invention; 3) determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time of filing (see MPEP §2163).

The Examiner has set forth a three factor analysis of written description compliance, choosing to look at the following factors: 1) field of the invention and predictability of the art; 2) breadth of the claims; 3) for each claimed genus/species, possession of claimed invention at the time of filing. Applicant is not aware of the basis for this written description analysis and respectfully requests the Examiner to provide an appropriate citation from either the MPEP or case law.

The Examiner has stated that Applicant has not provided adequate support for the breadth of the claims, alleging that a certain degree of specificity is required to produce each species of the claimed genus, and that Applicant would have to provide sufficient

evidence showing the production of multiple cross-linked HA wherein the HA molecules are cross-linked via more than two chemically distinct entities. Applicant respectfully disagrees.

Applicant respectfully submits that not only is the Examiner using the wrong analysis for written description, but that the Examiner is also improperly applying this analysis. Applicant would point out to the Examiner that claims 1-14 are process claims, and are not properly categorized as genus-species claims as the Examiner seems to have done. Accordingly, the third factor of the Examiner's three factor written description analysis does not apply to these claims. Claims 15 and 17-21 are product-by-process claims depending from process claim 1. These also do not fall under the genus-species analysis set forth by the Examiner.

With regard to claim 16, even assuming, *arguendo*, that the Examiner is correct in applying his three factor analysis, "[i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." The Regents of U. Cal. v. Eli Lilly, 119 F.3d 1559, 1568 (Fed. Cir. 1997). In the instant application, one could envision that the generic formula referred to by the Examiner is any compound comprising cross-linked HA, and that the species would be compounds comprising different cross-links. The Examiner has alleged that a certain degree of specificity is required to produce each species of the claimed genus. Applicant is unaware of a required degree of specificity other than that which could be readily ascertained through routine experimentation. One skilled in the

art at the time of filing would have had no problem in identifying the many species encompassed by the claims, as obtaining these species would merely have been a function of optimizing the reaction conditions disclosed.

For example, based upon the reagents and procedures disclosed in the specification and the claims, one skilled in the art would reasonably conclude that a composition with three, four, five or more different cross-links would be achievable simply by optimizing the reaction conditions and reagents disclosed through routine experimentation. It would not have been necessary to describe in detail the experimental conditions necessary to generate more than two cross-links, as "...the description only needs to describe in detail that which is new or not conventional." Hybritech at 1384. The Examiner has acknowledged that cross-linking was well known in the art, therefore a detailed description of the optimization steps would not be required. Accordingly, one of ordinary skill in the art at the time of filing would have realized that the invention of multiple cross-linked HA, with more than one type of cross-linking bond being present, was well within the possession of Applicant at the time of filing.

Thus, the remaining points that appear to be at issue in the pending application still seem to revolve around the enablement issues the Examiner initially set forth in the November 25, 2002 Office Action and appears to have maintained as part of the written description rejection. Applicant provided arguments in response to the enablement rejections, however the Examiner has not responded to those arguments in the most recent Office Action of May 20, 2003. We must therefore reiterate our arguments submitted in reply to said Office Action, further bolstering said arguments with additional experimental data submitted by Applicant herewith.

The Examiner has alleged that at each phase of the multi-step process, an additional set of concerns is raised, such as, types of bonds, catalysts, functional groups and cross-linking agents. Applicant maintains that these steps are merely routine optimization for one of ordinary skill in the art at the time of filing. Rather, optimization, common practice in the chemical arts, is all that would have been required and would not have been undue.

As was previously argued, the Examiner has acknowledged that cross-linking of HA is within the skill of the art at the time of filing. Applicant has demonstrated that multiple cross-links are possible, exemplifying this by showing double cross links, yet also providing adequate guidance to generate additional multiple cross-links for one of skill in the art at the time of filing. Specific exemplification of double cross-links does not preclude enablement of additional embodiments of the invention.

The Examiner has raised the issue of "undue experimentation." In assessing whether any necessary experimentation is undue, *Wands* set forth several factors to be weighed in making this determination. These factors include but are not limited to the following: The breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

As mentioned, the Examiner has acknowledged that cross-linked HA is known in the art, providing two exemplary documents (U.S. Patent Nos. 4,582,865 and 4,957,744). Applicant has also provided and discussed several exemplary documents in the

specification (see for example U.S. Patent Nos. 4,582,865; 5,550,187; 5,578,661; 5,644,049; 5,800,541; Tomihata *et al.*, J.Biomed.Mater.Res., 37, 243-251, 1997, and International Patent Application WO 97/04012) . Further, the Examiner has acknowledged that the level of ordinary skill in the art is high, stating that one with ordinary skill in the art would be an organic or polymer chemist having a M.S. degree or higher.

In the instant application, as the Examiner has noted, Applicant has provided several working examples demonstrating the production of double cross-linked HA. ***These examples demonstrate that the concept of multiple cross-linked HA, with more than one type of cross-linking bond being present, is a viable one.*** In no way, however, should they be construed to limit the scope of the present invention to that of only double cross-linked HA. The examples illustrate that the concept of more than one chemically distinct cross-links between HA is achievable. Progressing to the next step of more than two cross-links would have been well within the skill in the art at the time of filing by following the guidance set forth in the specification. The Examiner has provided no basis, either factual or legal, concerning why the guidance in the specification was <u>not</u> sufficient to produce more than double cross-linked HA.

Applicant has provided a sufficient amount of guidance in the specification for one skilled in the art to make not only double cross-linked HA, but multiple cross-linked HA. One issue that is examined with regard to enablement, is whether the materials required to make a compound or to practice a chemical process are disclosed in the specification. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). Applicant has provided, on page 6, lines 3-26 of the specification, several different types

of linkages, and the preferred cross-linking agent to be used to obtain these linkages. Further, the specification, beginning on page 6, line 28 and continuing to page 9, line 5, provides enough guidance to one skilled in the chemical arts to produce multiple cross-linked HA. As discussed *supra*, the necessary chemicals required for each type of cross-linking reaction have been provided by Applicant. Determining the specific order of the multiple reactions and the precise conditions was well within the skill of the art, and would have required only routine experimentation that would not have been undue for one skilled in the chemical arts at the time of filing, contrary to the Examiner's allegation.

Indeed, the experimental data submitted by Applicant herewith demonstrates that the specification provides enough guidance for one skilled in the chemical arts at the time of filing to produce multiple cross-linked HA (see Exhibit A). Under the section entitled "2. Synthesis Route of Multiple Crosslinked HA," synthesis Route 1 and Route 2 provide methods to generate multiple cross-linked HA using the standard chemical reactions disclosed in the specification. Applicant would direct the Examiner to the reagents used in this procedure, noting that all were disclosed in claims 4 and 7 of the pending application. By merely following the disclosure provided in the specification, Applicant has generated multiple cross-linked HA. Moreover, these multiple cross-linked HA display the desired properties described in the specification. Accordingly, in no way would the experimentation and optimization required to generate more than two cross-links be considered anything other than routine by one of skill in the art at the time of filing. If the Examiner is in disagreement with this position and maintains the rejection, he is requested to provide specific reasons why undue experimentation would be required.

In assessing whether the experimentation is undue, additional factors to look at are quantity of experimentation, time and expense, guidance, and difficulty of the experiments. MPEP §2164.06. Applicant has provided the necessary guidance to proceed with the production of multiple cross-linked HA, as discussed *supra*. The optimization of the different reaction conditions and reaction sequences would have been routine practice for one skilled in the chemical arts at the time of filing. Applicant has provided numerous working examples that provide guidance for the production of double cross-linked HA. Adding additional cross-linking steps to attempt to produce multiple (i.e. more than two) cross-linked HA would have imposed a minimal time and expense burden on the practitioner, and performing the assays necessary to verify the presence of multiple cross-linked HA would have been the same as the tests disclosed to assess the double cross-linked HA produced. The Examiner has failed to demonstrate that undue experimentation is required by the disclosure. Thus, Applicant maintains that no undue experimentation would have been necessary to practice the full scope of the invention at the time of filing.

Accordingly, when all of the relevant factors set forth in *Wands* are weighed, particularly noting the high level of skill in the art, the sufficient guidance provided in the specification, and that the experimentation entailed is not undue, Applicant maintains that the rejection under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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PROCESS OF MULTIPLE CROSSLINKED HYALURONIC ACID

SUPPLEMENTAL INFORMATION FOR US PATENT APPL.NO 09/920,286

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Abbreviations

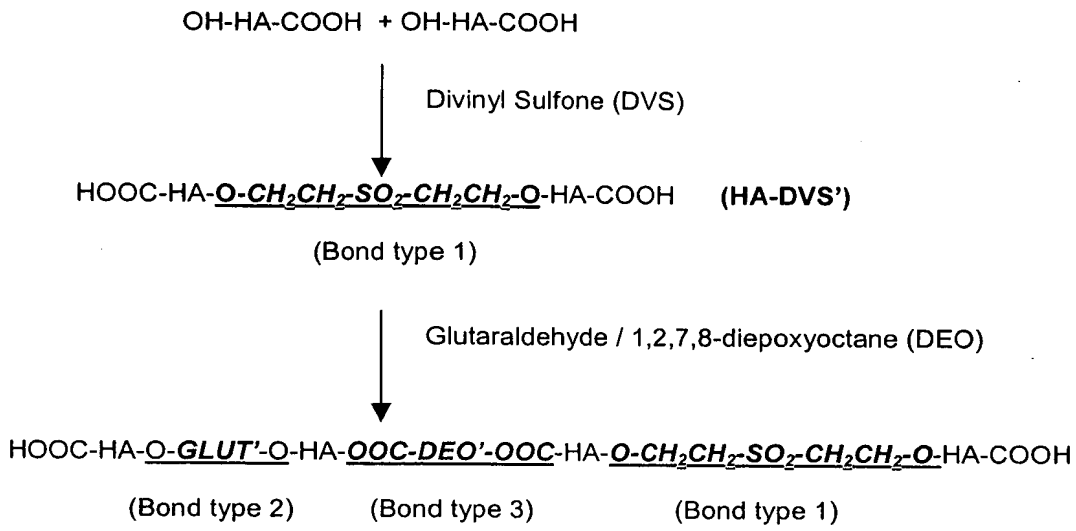
DVS': Bond type 1 built by reaction hydroxyl groups with DVS
Glut': Bond type 2 built by reaction with hydroxyl groups with glutaraldehyde
DEOAC: Bond type 3 built by reaction with carboxyl groups with DEO in acidic condition
DEOAL: Bond type 4 built by reaction with hydroxyl groups with DEO in alkaline condition
DEO: 1,2,7,8-diepoxyoctane
DVS: divinyl sulphone
Glut: glutaraldehyde

1. Introduction

Hyaluronic acid contains both hydroxyl and carboxyl functional groups, which can be used for crosslinking reactions. The crosslinkage formed between two HA molecules can be more than one type. In US Patent Appl. No. 09/920,286, two types of covalent bonds such as ether bond and ester bond have been introduced into the crosslinked network to form a double crosslinked HA. In this report, a multiple crosslinked HA, which has more than two types of bonds, has been prepared.

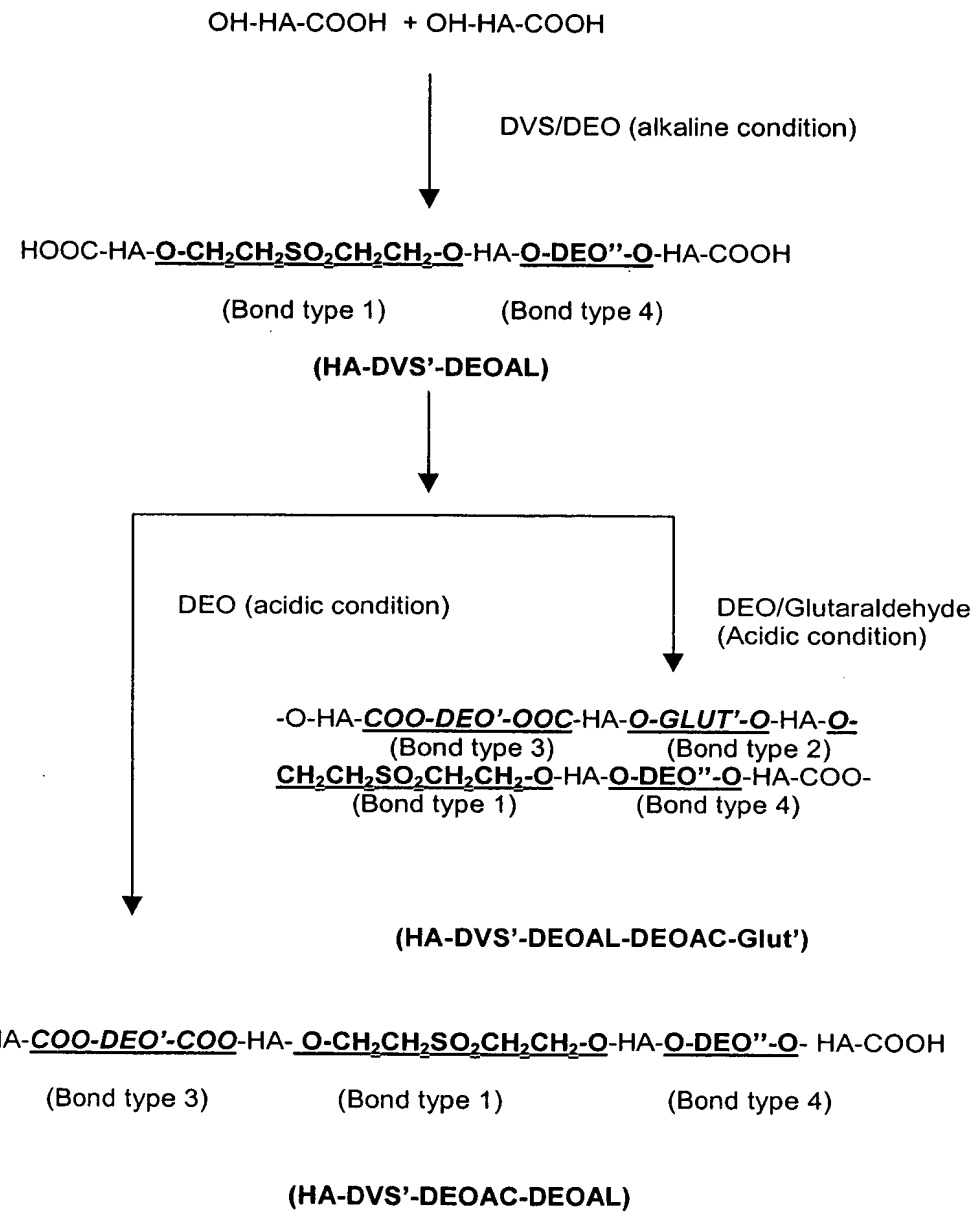
2. Synthesis Route of Multiple Crosslinked HA

Route 1:



(HA-DVS'-DEOAC-GLUT')

Route 2:


OH-HA-COOH + OH-HA-COOH
DVS/DEO (alkaline condition)
HOOC-HA-O-CH2CH2SO2CH2CH2-O-HA-O-DEO''-O-HA-COOH
(Bond type 1)
(Bond type 4)
(HA-DVS'-DEOAL)
DEO (acidic condition)
DEO/Glutaraldehyde
(Acidic condition)
-O-HA-COO-DEO'-OOC-HA-O-GLUT'-O-HA-O-
(Bond type 3)
(Bond type 2)
CH2CH2SO2CH2CH2-O-HA-O-DEO''-O-HA-COO-
(Bond type 1)
(Bond type 4)
(HA-DVS'-DEOAL-DEOAC-Glut')
OH-HA-COO-DEO'-COO-HA- O-CH2CH2SO2CH2CH2-O-HA-O-DEO''-O- HA-COOH
(Bond type 3)
(Bond type 1)
(Bond type 4)
(HA-DVS'-DEOAC-DEOAL)

3. Synth tic Method Examples

Example 1: (Control)

Single Crosslinking Using Divinyl Sulphone (DVS)

Weigh out 5g of dry solid HA and dissolve it into a 100ml 0.5M NaOH to obtain a 5% HA solution in alkaline condition. Divide above stock solution into two parts each containing 50ml stock solution. To one part add 0.38ml DVS, and to the other, add 0.19ml DVS, and mix. Cast the mixtures into a petri dish and dry for 24 hours in a fume-cupboard.

The dried film is neutralised using 5M HCl. The gel is purified using IPA and acetone and dried at room temperature under vacuum for 24 hours to obtain Single crosslinked HA using DVS named as HA-DVS'-1 and HA-DVS'-2. The water absorption capacity (WAC) and sulphur content were analysed as shown in Table 1 and Fig.1.

Table 1

Name	Batch Number	S content (%)	WAC(%)
HA-DVS'-1	Z1038	1.61	11155.67
HA-DVS'-2	Z1041	0.79	50664.00

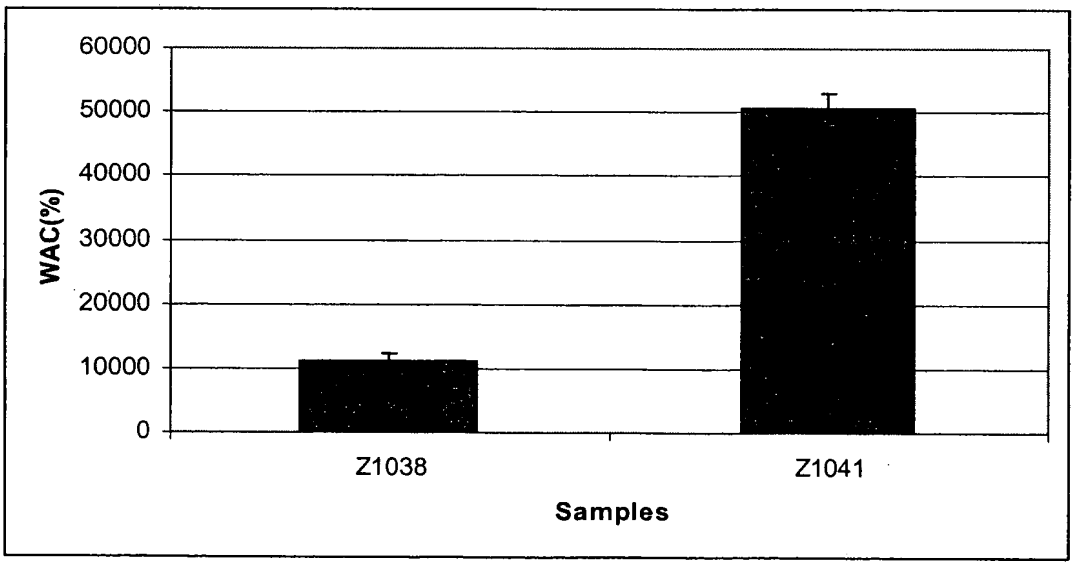


Fig.1 Comparison of WAC of DVS single crosslinked HA with different degree of crosslinking

Example 2:

100g of fully swollen DVS single crosslinked gel Z1041 was mixed with 1ml DEO. The pH of the gel was below 4. The mixture was cast into a petri-dish and dried for 24 hours to obtain HA-DVS'-DEOAC (double crosslinked HA). Similarly, 100g of Z1041 gel with pH below 4 was mixed with 1ml DEO and 1ml glutaraldehyde and cast into a petri-dish and dried for 24 hours to obtain HA-DVS'-DEOAC-Glut' (Triple crosslinked HA).

The dried material was purified using IPA (isopropyl alcohol) and vacuum dried for 24 hours. The S content and WAC results were shown in Table 2 and Fig.2.

Table 2

Name	Batch Number	S content (%)	WAC(%)
HA-DVS'	Z1041	0.79	50664
HA-DVS'-DEOAC	Z1059	0.52	1797.0
HA-DVS'-DEOAC-Glut'	Z1060	0.68	1483.0

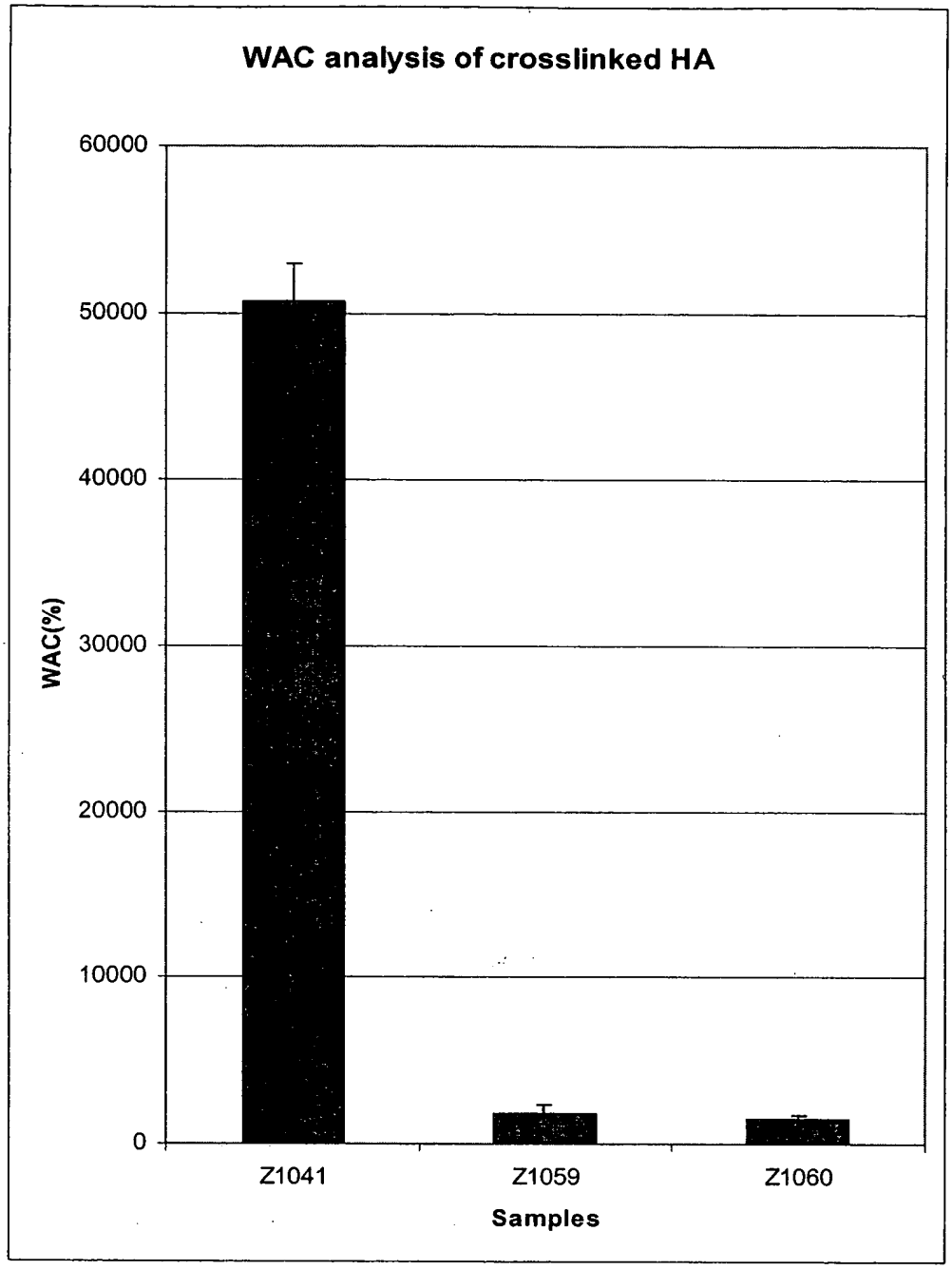


Fig.2 Comparison of WAC among single, double and triple crosslinked HA using combination of different crosslinking agents

Example 3

Table 3 shows the formulation design of multiple crosslinking process

Code No	Sample Name	Batch No	Crosslinking Agent
A	HA-DVS'	Z1047	DVS
B	HA-DVS'-Glut'	Z1048	DVS/GLUT
C	HA-DVS'-Glut'-DEO'	Z1049	DVS/GLUT/DEO
D	HA-DVS'-DEOAL	Z1050	DVS/DEO
E	HA-DVS'-DEOAL-Glut'	Z1051	DVS/DEO/GLUT
F	HA-DVS'-DEOAL-DEOAC	Z1052	DVS/DEO/DEO
G	HA-DVS'-DEOAL-DEOAC-Glut'	Z1053	DVS/DEO/DEO/GLUT

Preparation Method:

Sample A and D:

100ml of 5% HA in 0.5M NaOH was prepared according to the same method shown in Example 1. To 50ml of 5% HA, a certain amount of DVS was added and mixed. Then the mixture was cast into a petri-dish and dried over 48 hours. After drying, the mixture was neutralised using 5M HCl and washed using IPA

and acetone. **Sample A** was obtained. Similarly, to 50ml of 5% HA, certain amount of DVS and DEO were added and mixed. The mixture was cast into a

petri-dish and dried over 48 hours. After drying, the mixture was neutralised using 5M HCl and washed using IPA and acetone to obtain **sample D**.

Sample A: Single crosslinked, S%=0.49 , WAC(%) = 3294.3%
Sample D: Double crosslinked, S%=0.35 , WAC(%) = 1612.3%

Sample A and sample D were milled into particles using a mortar pestle and the crosslinked HA was subjected to further reaction.

Sample B:

Weigh out 0.5g of **A** into a glass universal, and add 10ml Acetone/0.1M HCl (7/3 v/v). To the universal, add 0.4ml of glutaraldehyde and react for 24 hours at room temperature. After reaction, wash the solid with IPA and acetone and dry under vacuum for 24 hours to obtain **sample B**.

Sample C:

Weigh out 0.5g of **A** into a glass universal, and add 10ml Acetone/0.1M HCl (7/3 v/v). To the universal, add 0.4ml of glutaraldehyde and 0.4ml DEO and react for 24 hours at room temperature. After reaction, wash the solid with IPA and acetone and dry under vacuum for 24 hours to obtain **sample C**.

Sample E:

Weigh out 0.5g of D into a glass universal, and add 10ml Acetone/0.1M HCl (7/3 v/v). To the universal, add 0.4ml of glutaraldehyde and react for 24 hours at room temperature. After reaction, wash the solid with IPA and acetone and dry under vacuum for 24 hours to obtain **sample E**.

Sample F:

Weigh out 0.5g of D into a glass universal, and add 10ml Acetone/0.1M HCl (7/3 v/v). To the universal, add 0.4ml of DEO and react for 24 hours at room temperature. After reaction, wash the solid with IPA and acetone and dry under vacuum for 24 hours to obtain **sample F**.

Sample G:

Weigh out 0.5g of D into a glass universal, and add 10ml Acetone/0.1M HCl (7/3 v/v). To the universal, add 0.4ml of glutaraldehyde and 0.4ml DEO and react for 24 hours at room temperature. After reaction, wash the solid with IPA and acetone and dry under vacuum for 24 hours to obtain **sample G**.

Table 4 and Fig.3 show the results of the water absorption capacity (WAC) of the crosslinked HA.

Table 4

			WAC(%)				
No	A(Z1047)	B(Z1048)	C(Z1049)	D(Z1050)	E(Z1051)	F(Z1052)	G(Z1053)
1	3187	4932	3301	1633	1482	1361	1335
2	3436	4633	3417	1519	1572	1383	1366
3	3260	5359	3186	1685	1746	1463	1538
Mean	3294	4975	3301	1612	1600	1402	1413
SD	128.0013	364.8758	115.5004	84.90779	134.2088	53.67805	109.3572

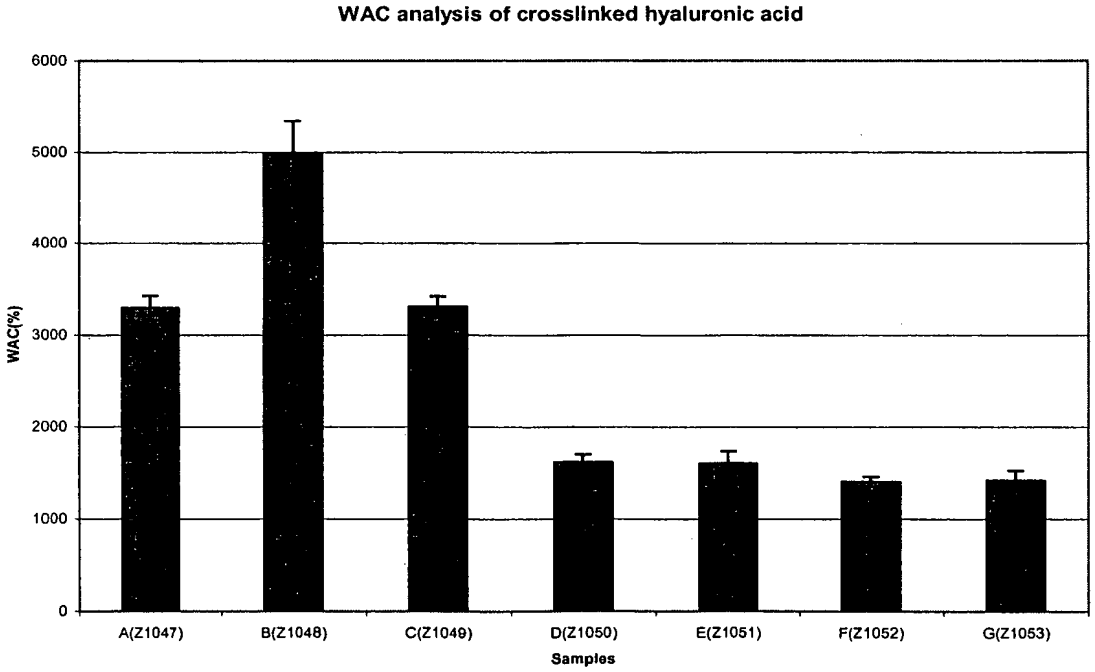


Fig.3 WAC analysis of crosslinked hyaluronic acid

Table 5 gives the results of sulphur content for the crosslinked HA, and shows that bond type 1 (apart from bond types 2, 3 and 4) was present in the network of all these crosslinked HA samples. Sulphur is not present in the native HA molecule.

Table 5 Sulphur content of crosslinked HA

Name	A	B	C	D	E	F	G
S content(%)	0.49	0.41	0.37	0.35	0.64	0.41	0.32

4. Discussion and Conclusion

In this report, four different types of covalent bonds were built into crosslinked HA networks, using different crosslinking reagents, or by using the same crosslinking reagent such as 1,2,7,8-diepoxyoctane (DEO) but changing the reaction conditions. The extra bond built into the network normally enhances the density of the network, which leads to a reduced water absorption capacity. The sulphur elemental analysis confirms that the sulphone ($-SO_2-$) bond is successfully incorporated into the crosslinking network.

The generation of bond types 1, 2, 3 and 4 resulted from standard chemical reactions, as shown in Section 2.

The reaction conditions, particularly the molar ratio of HA to the crosslinking reagent, can be varied to achieve the desired properties of the final products.